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Double Parathyroid Adenomas

Clinical and Biochemical Characteristics Before and After Parathyroidectomy

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Objective

There is considerable debate about whether double parathyroid adenomas are a discrete entity or represent hyperplasia with parathyroid glands of varying sizes. This distinction is important because it impacts on the extent of parathyroid resection and the success of the parathyroid operation.

Summary Background Data

Double parathyroid adenomas have been reported to occur in 1.7% to 9% of patients with primary hyperparathyroidism (HPT). It is important for surgeons to differentiate between double adenoma and hyperplasia with glands of varying sizes using gross examination during the initial procedure because microscopic findings of a small biopsy specimen at frozen-section examination may not be diagnostic.

Methods

From 1982 to 1992, 416 unselected patients (309 women and 107 men) with primary HPT without familial HPT or multiple endocrine neoplasia (MEN) were treated by one surgeon at the University of California at San Francisco. Double adenoma occurred in 49 patients, solitary adenoma in 309 patients, and hyperplasia in 58 patients. The authors analyzed the clinical manifestations, the preoperative and postoperative serum levels of calcium, phosphate, and parathyroid hormone (PTH), and the success rate and outcome after parathyroidectomy and compared their results in 49 patients with double adenomas to the results for patients with solitary adenomas or hyperplasia.

Results

Ten of the patients with double adenomas (20.4%) were referred for persistent HPT after removal of one abnormal parathyroid gland. The ages of the patients with double adenoma, single adenoma, and hyperplasia were 61 ± 14, 56 ± 15, and 58 ± 7 years, respectively. Fatigue, muscle weakness, and bone pain were common in patients with double adenomas, whereas nephrolithiasis occurred more frequently in patients with solitary adenoma ($p = 0.0001$). Serum calcium and PTH levels (per cent of upper limit of normal) fell from 11.5 ± 1.2 mg/dL and 487% to 9.5 ± 0.8 mg/dL and 61% for patients with double adenomas; from 11.4 ± 0.9 mg/dL and 378% to 9.3 ± 1.4 mg/dL and 101% for patients with single adenoma; and from 10.9 ± 0.5 mg/dL and 418% to 9.1 ± 0.7 mg/dL and 94% for patients with hyperplasia, respectively. There was no recurrence in the patients with double adenomas with a mean follow-up time of 5.8 years.

Conclusions

Double adenomas are a discrete entity and occur more often in older patients. Patients with double adenomas can be successfully treated by removal of the two abnormal glands.

An important question concerning the management of patients with primary hyperparathyroidism (HPT) is whether all patients with more than one abnormal parathyroid gland have hyperplasia or do some have multiple adenomas? If a surgeon fails to remove abnormal parathyroid glands, HPT will persist or recur. Of equal or greater concern is that if a surgeon removes too many parathyroid glands, permanent HPT will develop. Multiple abnormal parathyroid glands have been reported to occur in 6.8% to 39% of patients with primary HPT,[1-3] whereas double parathyroid adenomas have been reported to occur in 1.7% to 9% of patients.[4-11] Operative criteria used to distinguish between normal and abnormal parathyroid glands include (1) weight of more than 65 mg, (2) size larger than 7 mm, (3) a darker beige or brown color, and (4) gland firmness. Histologic criteria include hypercellularity and the amount of intercellular and intracellular fat. It is important for surgeons to differentiate between double adenoma and hyperplasia with glands of varying sizes using gross examination during the initial procedure because microscopic findings of a small biopsy specimen at frozen-section examination may not be diagnostic. Sometimes it is difficult to differentiate microscopically between normal and abnormal parathyroid glands and it is currently impossible to differentiate between an adenoma and a hyperplastic parathyroid gland, unless a normal parathyroid gland is also identified. Furthermore, focal microscopic hypercellularity may be present in normal-appearing, normal-sized parathyroid glands in patients with a single adenoma. These hyperplastic parathyroid glands of normal size are of little clinical importance.[12,13] Today, there is no consensus as to whether double parathyroid adenomas are a distinct entity or whether they represent asymmetrical diffuse hyperplasia.[14-16] Previous articles, however, have suggested that double adenomas are a distinct entity.[4-11]

In this article, we report our experience in 49 patients with double adenomas to determine whether double adenomas are a distinct clinical entity or are hyperplastic glands of variable size. We were also interested in documenting whether the clinical manifestations of patients with double adenomas differ from those found in patients with solitary adenoma or hyperplasia.

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METHODS

We studied the medical records of 416 unselected patients (309 women and 107 men) with primary HPT who were treated by one of us (O.H.C.) at the University of California Hospitals between 1982 and 1992. Patients with familial HPT or multiple endocrine neoplasia (MEN) types 1 and 2 were excluded due to existence of multigland disease.[17] Solitary adenoma occurred in 309 patients (74.3%), parathyroid hyperplasia in 58 patients (13.9%), and double adenomas in 49 patients (11.8%). Ten patients (20%) were referred for persistent primary HPT after one parathyroid tumor had previously been removed; they were found to have a second adenoma. We analyzed the clinical manifestations, the preoperative and postoperative serum levels of calcium, phosphate, and parathyroid hormone (PTH), and the success rate and outcome after parathyroidectomy. When ten patients who were referred for persistent HPT were excluded, the incidence of double adenomas was 9.4%. We compared our results in 49 patients with double parathyroid adenomas to those for patients with solitary adenomas or hyperplasia. All patients had the diagnosis of primary HPT established by documentation of an elevated serum parathyroid (PTH) level in a hypercalcemic patient, and many of the patients also had hypophosphatemia. A standard questionnaire of symptoms was administered at the initial preoperative office visit and at postoperative follow-up visits.[18] The questionnaire was completed 1 to 4 weeks and then 6 months after parathyroidectomy; this was repeated at 1-year intervals thereafter. During the follow-up period, all patients had serum levels of PTH, calcium, and phosphorus analyzed. Because several PTH assays (including midregional radioimmunoassay and intact immunoradiometric or immunochemoluminescent assays) were used during the follow-up period of these patients,[19,20] the levels of PTH were standardized as the percentage of the upper limit of normal in a particular assay. Bilateral neck exploration is our standard initial surgical approach in virtually all patients with HPT because it is safe and it is most likely to result in a successful operation.[21] When one abnormal gland was identified (single adenoma), it was excised and confirmed by frozen-section examination and a biopsy was performed on one normal gland. When two abnor-

mal parathyroid glands and two normal parathyroid glands were identified (double adenomas), the two abnormal glands were removed and a biopsy was usually performed on normal glands that were marked with a silver clip. When all the parathyroid glands were abnormal (hyperplasia), a subtotal parathyroidectomy (resecting 3½ glands) and bilateral thymectomy was the routine operative procedure. In patients with diffuse hyperplasia, a biopsy was performed on the smallest of the hyperplastic glands that was not immediately adjacent to the recurrent laryngeal nerve, leaving about a 50- to 60-mg parathyroid remnant. After confirming at frozen-section examination that this gland was hypercellular parathyroid tissue and viable, the other three abnormal glands were resected. For this study, the diagnosis of double adenomas was based on the surgical finding of two abnormal and two or more normal parathyroid glands at the initial parathyroid operation with histologic confirmation and subsequent normocalcemia, or in patients requiring reoperation the histologic documentation of one abnormal and usually one normal parathyroid gland at the initial operation and one abnormal parathyroid gland at the second operation with subsequent normal serum calcium levels. PTH levels were also normal in most patients (n = 43), but not all (n = 6).

Results are expressed as the mean ± standard deviation. Statistical analysis was performed using the chi square contingency table, Fischer's exact test, and the analysis of variance (ANOVA).

RESULTS

Double adenomas were found in 42 women (86%) and 7 men (14%), single adenomas were identified in 226 women (73%) and 83 men (27%), and hyperplastic parathyroid glands were found in 41 women (71%) and 17 men (29%). The ages of the patients with double adenomas, single adenomas, and hyperplasia were 61 ± 14, 56 ± 15, and 58 ± 17 years, respectively (Table 1). Patients with double adenomas were older than patients with single adenomas ($p < 0.001$). Sixty-one per cent of patients with double adenomas were older than 60 years, 46% of patients with single adenomas were older than 60 years, and 52% of patients with hyperplasia were older than 60 years.

Table 1. PATIENT CHARACTERISTICS ACCORDING TO HISTOPATHOLOGY (AGE AND SEX OF 416 UNSELECTED PATIENTS)

	No.	Age (Mean ± SD)	No. of Men (%)	No. of Women (%)
Double adenomas	49	61 ± 14	7 (14)	42 (86)
Single adenoma	309	56 ± 14	83 (27)	226 (73)
Hyperplasia	58	58 ± 17	17 (29)	41 (71)
Total	416	57 ± 15	107 (26)	309 (74)

Table 2. FREQUENCY OF SYMPTOMS BEFORE AND AFTER SURGERY IN DOUBLE ADENOMAS, SINGLE ADENOMA, AND HYPERPLASIA

	Double Adenomas (n = 49)		Single Adenoma (n = 309)		Hyperplasia (n = 58)	
	Preop (%)	Postop (%)	Preop (%)	Postop (%)	Preop (%)	Postop (%)
Fatigue	80*	19	65	13	66	10
Muscle weakness	73*	20	54	13	43	5
Joint pain	53	25	50	12	43	7
Bone pain	53*	16	41	12	41	14
Neuropsychiatric disorder	41	8	39	12	45	9
Nocturia	35	8	35	6	35	4
Polyuria	35	6	33	6	29	4
Constipation	33*	10	30*	7	19	2
Memory loss	29	6	27	6	28	7
Weight loss	25	6	23	3	24	0
Pruritus	14	2	11	3	9	2

* $p = 0.0001$.

Preoperative Clinical Presentations

The preoperative symptoms and associated conditions of patients with double adenoma, single adenoma, and parathyroid hyperplasia are shown in Tables 2 and 3. Fatigue, muscle weakness, and bone pain were more commonly observed in patients with double adenomas than in patients with single adenomas or hyperplasia ($p = 0.0001$). Constipation occurred more frequently in patients with double or single adenoma than in patients with hyperplasia ($p = 0.0001$). Joint pain was observed more frequently in patients with double adenomas than in patients with hyperplasia, but this difference was not significant (Table 2). Preoperative associated conditions in double adenomas did not differ from those of patients with solitary adenomas or hyperplasia, with the exception that kidney stones were more common in patients with solitary adenoma ($p = 0.0001$) (Table 3). Pancreatitis occurred more often in patients with single adenoma than in patients with hyperplasia. No patients with double adenomas experienced pancreatitis. Gout occurred in fewer than 10% of patients with double adenomas, single adenomas, or hyperplasia. A history of exposure

Table 3. FREQUENCY OF ASSOCIATED CONDITIONS BEFORE AND AFTER SURGERY IN DOUBLE ADENOMAS, SINGLE ADENOMA, AND HYPERPLASIA

	Double Adenomas (n = 49)		Single Adenoma (n = 309)		Hyperplasia (n = 58)	
	Preop (%)	Postop (%)	Preop (%)	Postop (%)	Preop (%)	Postop (%)
Hypertension	41	12	40	17	38	14
Nephrolithiasis	14	4	28*	14	11	3
Peptic ulcer disease	16	2	12	1	14	2
Pancreatitis	0	0	8	0	3	0
Bone fracture	10	0	8	0	10	0
Gout	4	2	7	1	9	2

* $p = 0.0001$.

to low-dose therapeutic radiation to the neck existed for 12% of patients with double adenoma, 10% of patients with single adenoma, and 8% of patients with hyperplasia.

Preoperative Laboratory Findings

The preoperative serum calcium, PTH, and phosphorus levels are shown in Table 4. Serum calcium and phosphorus levels in double adenomas did not differ from those for patients with single adenoma or hyperplasia. However, preoperative serum PTH values were higher in patients with double adenomas than in patients with single adenoma or parathyroid hyperplasia ($p < 0.001$). The preoperative mean serum alkaline phosphatase levels were 148 IU/L for double adenomas, 123 IU/L for single adenomas, and 99 IU/L for hyperplasia. An increased serum chloride to phosphate ratio (normal, < 33) was found in 26 of 32 patients with double adenomas. Preoperative imaging studies including ultrasonography and thallium technetium scanning were done in 39 patients. Although one abnormal parathyroid gland was identified in 77% of patients with double adenomas, both abnormal parathyroid glands were identified in only 6 patients (15%).

Operative Findings and Treatment

Double adenomas were present on both sides of the neck in 55% of the patients. Double adenomas were situated in the right lower location (31%), right upper location (30%), left upper location (21%), and left lower location (11%). Six per cent were intrathymic and 1% were intrathyroidal. Thus, about two thirds of the double adenomas were situated on the right side of the neck. At operation, hypercellular parathyroid tissue confirmed at frozen-section examination was excised from every patient (Fig. 1). Two patients had cystic, enlarged parathyroid adenoma containing between 2 and 9 mL of fluid, but the other parathyroid glands were normal. The weights of the adenomas ranged from 75 to 2300 mg (mean, 452 mg), excluding one microadenoma with a weight of 25 mg. The mean size of the double adenomas was 1.5 cm (range, 0.7 to 3.4 cm), excluding one microadenoma with a mean size of 0.3 mm. Postoperative surgical complications among the 416 patients included one case of transient vocal cord palsy (0.2%), six cases of transient hypocalcemia (1.4%), and two cases requiring evacuation of wound hematomas (0.5%).

Postoperative Clinical Presentations and Laboratory Findings

Symptoms and associated conditions decreased in patients in all groups after surgery. Postoperative clinical manifestations in patients with double adenomas are seen in Tables 2 and 3. The postoperative serum levels of calcium, PTH, and phosphorus are shown in Table 4. The postoperative levels of calcium and PTH decreased

Table 4. PREOPERATIVE AND POSTOPERATIVE LABORATORY VALUES

	Serum Calcium (8.5–10.5 mg/dL)		Serum PTH (% ULN)		Serum Phosphorus (3.0–4.5 mg/dL)	
	Preop	Postop	Preop	Postop	Preop	Postop
Double adenomas	11.5 ± 1.2*	9.5 ± 0.8	487 ± 106†	61 ± 13	2.55 ± 0.5	3.36 ± 0.3
Single adenoma	11.4 ± 0.9	9.3 ± 1.4	378 ± 143	101 ± 26	2.53 ± 0.5	3.09 ± 0.4
Hyperplasia	10.9 ± 0.5	9.1 ± 0.7	418 ± 122	94 ± 17	2.77 ± 0.6	3.2 ± 0.7

ULN: upper limit of normal.
* Mean ± SD.
† $p < 0.001$.

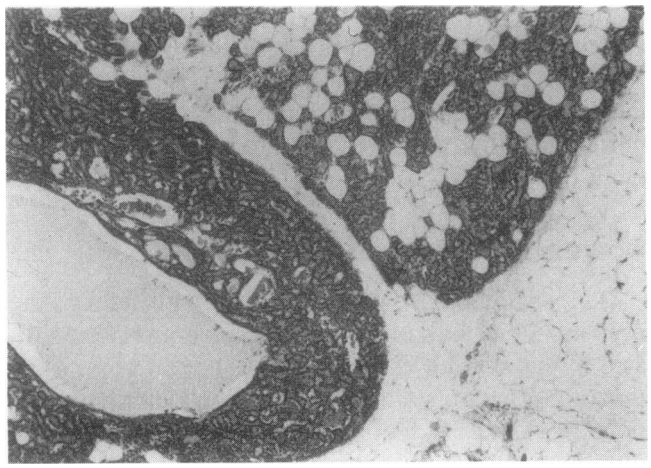

Figure 1. Hypercellular parathyroid parenchyma in a 62-year-old woman with double adenomas (H&E, ×125)

in all patients with double adenomas (Fig. 2). Serum calcium levels normalized postoperatively and remained normal for 36 months or longer (mean follow-up, 5.8 years) (Fig. 3A). Serum PTH levels were initially normal, increased at 6 months, and then decreased (Fig. 3B). Six patients had elevated serum PTH values after parathyroidectomy, but in five of these the calcium level was less than 9.0 mg/dL. There was no statistical difference in

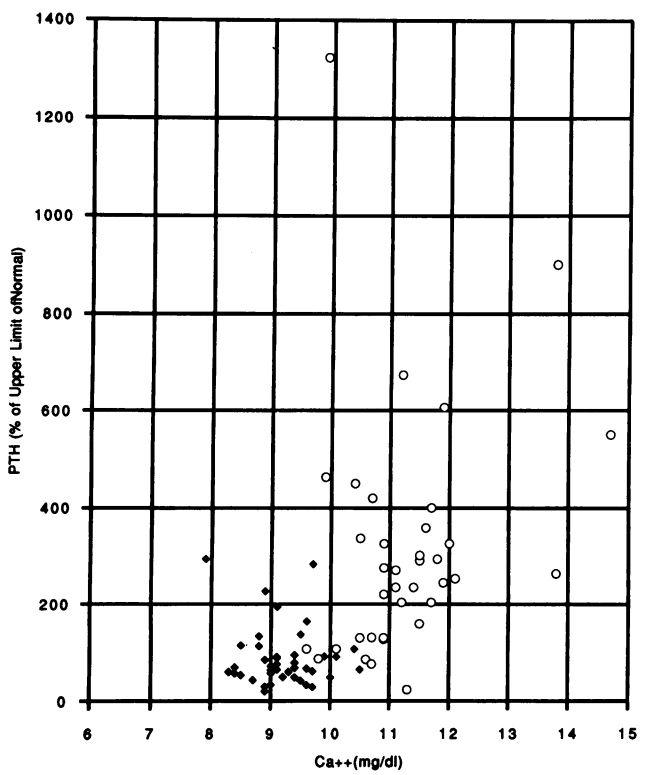

Figure 2. Preoperative and postoperative serum calcium and PTH values in double adenomas. o: Preoperative values; •: postoperative values.

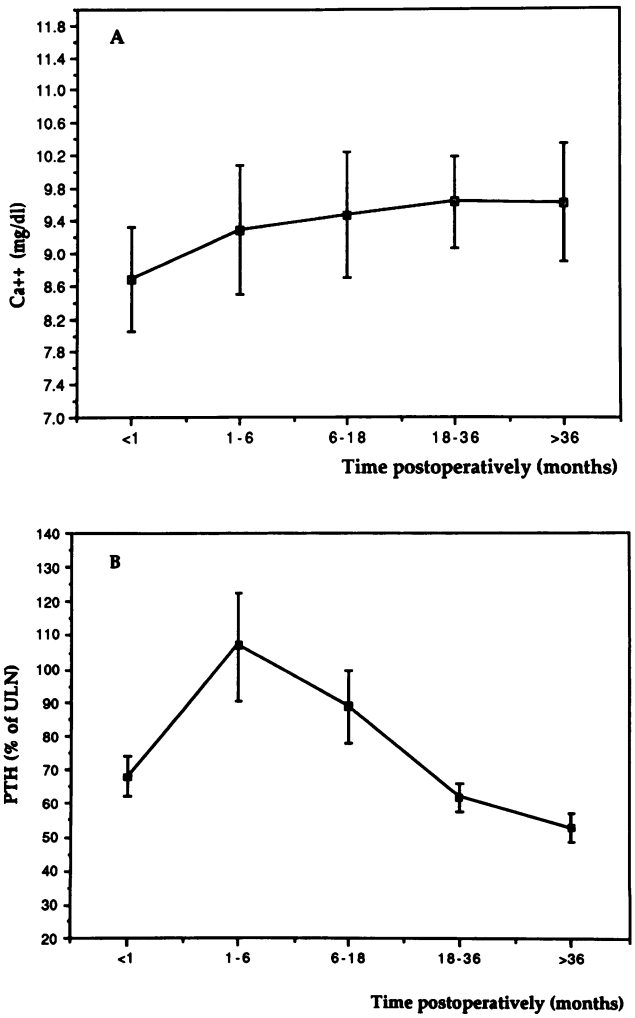

Figure 3. (A) Postoperative serum calcium values in double adenomas. Each point on the curve shows serum calcium levels measured at different times during follow-up. (B) Postoperative serum PTH values in double adenomas. Each point on the curve shows serum PTH levels measured at different times during follow-up.

postoperative serum laboratory tests between the three groups.

Outcome

There were no recurrences among patients initially treated by us for double adenomas or single adenoma with a mean follow-up period of 5.8 years (range, 6 months to 10 years). Two of our patients with parathyroid hyperplasia, however, required re-exploration because of persistent hypercalcemia. These two patients had ectopically situated parathyroid glands in the mediastinum, one intrathymic, and one had a fifth gland in a paraesophageal position. Overall, 414 of 416 patients and all patients with double adenomas have become and remained normocalcemic.

DISCUSSION

In this investigation, we evaluated the clinical manifestations before and after parathyroidectomy in patients with primary HPT who had double parathyroid adenomas and compared them to those of patients with primary HPT who had either a single adenoma or parathyroid hyperplasia. Patients with primary HPT and double adenomas were slightly older than patients of the other two groups. We previously reported that double adenomas occurred more frequently in older patients (> 60 years; 9.3%) than younger patients (< 60 years; 2.5%).[22] Fatigue, muscle weakness, and bone pain were more common in patients with double adenomas than patients with single adenoma or hyperplasia. This is possibly secondary to a more severe HPT despite similar serum calcium levels as suggested by the higher PTH and alkaline phosphatase levels in patients with double adenomas than in patients of the other groups. Other clinical manifestations were similar in the three groups, except that kidney stones occurred more frequently in patients with solitary adenomas. Patients in all three groups had fewer symptoms after surgery.

We found a high incidence (11.8%) of double adenomas in patients with primary HPT. This incidence is higher than what other investigators have reported, and perhaps reflects our referral bias and older patient population. When the ten patients (20%) who were referred due to persistent or recurrent disease were excluded, the incidence of double adenomas in our series was 9.4%. In 1954, Wermer[23] described an incidence of 5% for double adenomas in his series. In 1958, Cope et al.[14] suggested that primary chief-cell hyperplasia of the parathyroid glands was a common cause of HPT, especially in patients with MEN and even nonfamilial HPT. Wang and Rieder[16] have suggested that the "so called" double adenomas are very rare and are in reality asymmetrical hyperplasia. They have recommended unilateral neck exploration when a single adenoma is found in one side and the other parathyroid gland appears to be normal. Harness et al.[8] described a 1.7% incidence of double adenomas. They excluded patients with a family history of MEN or familial HPT, but required histologic confirmation of two normal glands in addition to postoperative normocalcemia. Roses et al.[5] reported a 8.6% incidence of double adenomas and suggested that excision of both enlarged glands, even if they are asymmetrical, is appropriate. Attie et al.[6] described a 3.8% incidence of double adenomas and recommended removal of only grossly enlarged parathyroid glands in patients with HPT. Brothers and Thompson[11] reported a 9% incidence of double adenomas in patients older than 65 years. Patients with MEN and familial primary HPT have a higher incidence of multiple abnormal parathyroid glands including double adenomas, although most have hyperplasia with varying gland size.[17] Multiple, enlarged parathyroid glands in patients with MEN have been reported to occur in 50% to 77% of patients.[24–26] The existence of double adenomas seems indisputable based upon operative and histologic findings and more importantly on long-term follow-up documentation of postoperative serum calcium and PTH levels. Therefore, it is important for surgeons to differentiate between normal and abnormal parathyroid glands. Frozen-section analyses can confirm that the removed tissue is parathyroid, but cannot differentiate between adenoma and hyperplasia. Hypercellularity helps to differentiate between abnormal and normal parathyroid tissue, but it is not completely reliable.[12] Normal parathyroid glands can also have areas of focal hyperplasia that are usually of no clinical consequence.[4,12,13] The finding of a slightly enlarged parathyroid gland in a patient with profound hypercalcemia or markedly elevated PTH levels suggests that one or more other abnormal parathyroid glands are still present.[27] Although it is usually not difficult to recognize double adenomas, it is occasionally difficult to distinguish between this condition and asymmetric hyperplasia. Thus, the surgeon must be able to recognize the difference between double adenomas, asymmetrical hyperplasia, and one adenoma coexisting with an enlarged, fatty, normal parathyroid gland. In addition to size, color and firmness help make this distinction. Intracellular lipid staining with osmium carmine or oil red O has been used to document the amount of extracellular and intracellular fat in order to distinguish hyperplasia from adenoma and normal from abnormal, but it is not always effective.[28] Because primary hyperplasia is more common than double adenomas, any patient with more than one abnormal parathyroid gland must be assumed to have diffuse hyperplasia until two normal glands have been identified.

Bilateral neck exploration is our standard surgical approach for virtually all patients with HPT who are undergoing initial operation. Identification of all of the parathyroid glands makes it easier to differentiate between double adenomas and diffuse hyperplasia. Our surgical approach for patients with double adenomas is resection of the two enlarged glands with histologic confirmation by frozen-section examination of these glands and a small biopsy specimen from normal glands. When a biopsy is performed on the normal glands, one must be careful to avoid injury or devascularization of the gland. In patients with parathyroid hyperplasia, our policy is to perform subtotal parathyroidectomy (resecting 3½ glands) and bilateral thymectomy. The latter is done because supernumerary glands are frequently (15%) found in the thymus or perithymic fat.[29] Some surgeons advocated 3½ gland parathyroidectomy or total parathyroidectomy and autotransplantation for patients with double

adenomas.[1,7,30] We believe that this is overtreatment and may result in permanent hypoparathyroidism. All of our 49 patients with double adenomas are normocalcemic after selective resection of enlarged glands. Hypoparathyroidism is a worse complication than either persistent or recurrent HPT because the latter conditions can almost always be successfully corrected. We routinely cryopreserve parathyroid tissue in patients with hyperplasia and in all patients who undergo parathyroid reoperations as insurance against possible permanent hypoparathyroidism. If hypoparathyroidism were to develop, the cryopreserved parathyroid tissue could be autotransplanted.

Preoperative localizing tests in patients with multiple abnormal glands are usually not helpful because they only identify about 20% to 30% of all the abnormal glands.[31,32] Bonjer et al.[33] studied parathyroid glands from 274 patients, who were observed for 13.5 years, using DNA flow cytometry. They suggested that flow cytometric DNA analysis could objectively differentiate abnormal glands from normal glands. However, it was not possible to differentiate single gland disease from multigland disease. Postoperative serum calcium values appear to be the most important predictor for recurrent or persistent parathyroid disease in the early postoperative period. Duh et al.[27] suggested that preoperative serum immunoreactive PTH (iPTH) measurement is a very sensitive diagnostic test for primary HPT, but postoperative serum iPTH measurement in a normocalcemic patient is not a good predictor for recurrent or persistent HPT. The serum iPTH level (using mid or C terminal radioimmunoassays) can remain high for up to 6 months in 40% of patients despite successful parathyroidectomy and normocalcemia, and this occurred in six of our patients. Causes for increased PTH values include bone hunger, hypercalciuria, malabsorption, and renal dysfunction. The latter condition is eliminated as a cause for elevated PTH levels by using intact or two site PTH assays.[19,20,27] We do not know why some patients with nonfamilial primary HPT have single, double, or even triple adenoma. Byström et al.[34] have documented an abnormality in the short arm of chromosome 11 in patients with MEN 1 that is also found in 29% of parathyroid glands from patients with sporadic primary HPT. Arnold et al.[35] found inversion mutation involving oncogene PRAD-1 in some parathyroid adenomas. Backdahl et al.[36] suggested that many or all solitary sporadic parathyroid adenomas were monoclonal, whereas multiple gland involvement or nonfamilial primary hyperplasia was probably a polyclonal process. Information concerning clonality of parathyroid tumors is controversial.[35,37]

To the best of our knowledge, the current series is the only report documenting preoperative and postoperative serum calcium, phosphorus, and PTH levels in patients with double parathyroid adenomas. The operative findings, histology, and long-term serum calcium and PTH values document that double adenomas are a discrete clinical entity and occur more often in older patients. Successful treatment results from removal of the two abnormal glands, whereas patients with parathyroid hyperplasia require a subtotal parathyroidectomy. Because multiple abnormal parathyroid glands occur in up to 25% of patients, bilateral neck exploration should be the treatment of choice for virtually all patients to avoid persistent or recurrent HPT.

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Discussion

R. WILLIAM C. MCGARITY (Atlanta, Georgia): I enjoyed this interesting paper. In patients with primary hyperparathyroidism, there has been a problem in determining the pathology in those who have two and three enlarged glands when the other gland or glands were normal. The authors have given us their criteria that was used in determining the diagnosis of double adenomas.

There seems to be an increasing number of patients with two and three enlarged glands. Many of these patients have been diagnosed as having nodular hyperplasia. Our instance of hyperplasia is high because our pathologist diagnosed most patients with multiglandular disease as having diffuse or nodular hyperplasia rather than multiple adenomas. In our series of patients with primary hyperparathyroidism, about one-third had diffuse or nodular hyperplasia, and two-thirds had a single adenoma. In the past, we have performed subtotal resection in patients with multiglandular disease.

In the paper that we have heard today, I think it is of interest that there has been no recurrence in patients who had a double adenoma, with a mean follow-up time of 5.8 years.

I would like to ask if the authors have seen or had a diagnosis of three adenomas in a patient, and do they think that the follow-up time is long enough to determine the true rate of recurrence?

I appreciate the opportunity to discuss this paper.

DR. WILLIAM SILEN (Boston, Massachusetts): I'd like to thank Dr. Clark for the privilege of reviewing his manuscript before the meeting.

I rise to concur with the proposal of Dr. Clark's group that there really is a distinct entity and a distinct group of patients with two-gland enlargement. In a smaller series, we've had exactly the same experience; namely, that these patients are cured by removal of the two abnormal glands.

This has important implications regarding those who advocate unilateral exploration in patients with primary hyperparathyroidism, and we agree with Clark's group that bilateral exploration is preferable since more than half of their patients and more than half of ours with double lesions have had bilateral lesions.

We've been struck by one finding in our group of patients with double adenoma; namely, that a reasonably consistent finding has been that most of them have been on very long-term chlorothiazide therapy for 10 to 12 years before the development of persistent primary hyperparathyroidism. I wonder if they've noted the same finding?

DR. EDWIN L. KAPLAN (Chicago, Illinois): This study is very commendable for it demonstrates, as do two or three other recent papers including our own, an early cure rate of 98% to 99% of patients operated on for primary hyperparathyroidism, if patients with the MEN syndromes and familial hyperparathyroidism are excluded. These excellent results are due in part to improved diagnosis using the intact parathyroid hormone assay, but they certainly reflect the careful, meticulous technique used by very experienced surgeons.